

REVIEW

The First U.S.-Japan Teratology Seminar, 1965

Robert W. Miller

National Cancer Institute, Clinical Genetics Branch, Bethesda, Maryland, USA

ABSTRACT A U.S.-Japan Seminar on was held in Tokyo on November 1-5, 1965 on "Epidemiological Studies into the Etiology of Congenital Malformations and Cancer." It was convened by Dr. Hideo Nishimura of Kyoto University and Dr. Robert W. Miller of the National Cancer Institute (NCI). The main purposes were to introduce teratologists from the two countries to one another and to seek new areas of research. Among the assets for research in Japan were 1) Dr. Nishimura's collection of embryos for studies of normal intrauterine growth and for studies of congenital malformations among spontaneous miscarriages; 2) the availability of standard occupational records for information related to reproductive performance; 3) the family registry (*koseki*), useful for follow-up studies, vital events and evidence of consanguinity; 4) the Metropolitan Tokyo Children's Cancer Registry which soon after was extended to 5 more metropolitan areas; 5) the annual publication of autopsy summaries; 6) data from the (U.S.-Japan) Atomic Bomb Casualty Commission in Hiroshima and Nagasaki; 6) death-certificate diagnoses for migrants from Japan to the U.S. among whom studies of changes in cancer rates had been initiated at the NCI. Also in Japan 7% of marital partners were second-cousins or closer, of interest in studying genetic effects on the occurrence of cancer or congenital malformations. The seminar was followed by a workshop on methods in teratology held in Kyoto in 1968. These meetings led to progressive increases in the exchange of scientists and information.

Key words: cancer, teratology, epidemiology, etiology, embryology, consanguinity, *koseki* record, history

INTRODUCTION

In 1964 I described my interest in teratology to a genealogist at a Bethesda dinner party. He said that Dr. Nishimura, a leading Japanese teratologist, was to visit him next week in Washington, and he arranged for us to meet. Dr. Nishimura and I saw the value of holding a symposium in Japan on 1) birth

defects and 2) childhood cancer, each of which had been induced by ionizing radiation (Miller, 1964), and each of which occurred excessively with the other in certain genetic disorders; *e.g.*, leukemia with Down syndrome (Miller, 1964), and Wilms' tumor in children born with aniridia (absent irises) (Miller *et al.*, 1964).

FUNDING

The search for funding led me to the National Science Foundation, which had a U.S.-Japan Program for basic sciences and for special topics such as predicting earthquakes. Our subject was outside the scope of NSF support, but fortunately funds were provided for five U.S. scientists to travel to Tokyo for the symposium. The expenses of other scientists were covered by the National Cancer Institute and by the Atomic Bomb Casualty Commission in Hiroshima. Dr. Nishimura obtained funds from the Japan Society for the Promotion of Science to host the meeting and to cover the cost of the Japanese participants. The meeting was held on November 1-5, 1965 at the well-appointed International House of Japan, which included facilities for housing and dining. It was attended by 18 Japanese and 16 Americans.

THE MEETING

The 5-day meeting allowed the participants to express themselves freely. There was time for discussions after each presentation, and five hours at the end for general discussion. The journal, *Science*, had just declared an end to publication of meeting reports, but the Editor agreed to publish one more, ours (Miller and Nishimura, 1966).

A main objective of the symposium was to introduce scientists from the two countries to one another in the fields of teratology, pediatric oncology and epidemiology. Teratogenesis and carcinogenesis have features in common that can be revealed by epidemiology. Research into one has revealed etiologic information concerning the other. For example, a deletion on chromosome 13 found in children with the neoplasm and a syndrome of skeletal defects and mental retardation indicated the location of the retinoblastoma gene; and a Wilms tumor gene (*WT-1*) was located through a deletion on chromosome 11 that is contiguous with the gene for congeni-

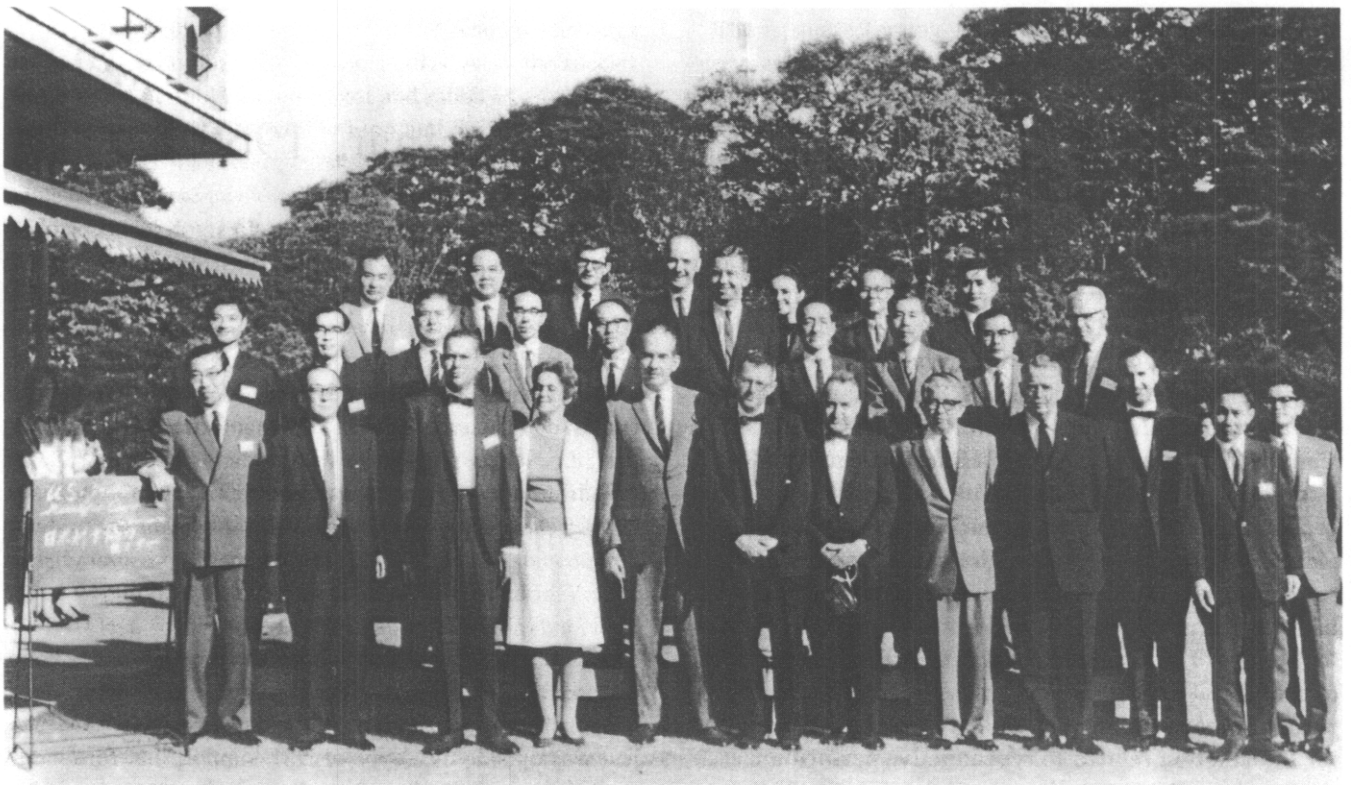


Fig. 1 Outside the International House of Japan, Roppongi, Tokyo, November 7, 1965: Participants in the Seminar on the epidemiology of cancer and congenital malformations.

tal aniridia (both were in the same deletion). These observations led Knudson in 1971 to propose the concept of tumor suppressor genes, which when deleted, can no longer perform their function of controlling normal growth—and neoplasia ensues (reviewed by Knudson, 1995). Thus, study of rare occurrences of certain childhood cancers associated with congenital malformations has led to recognition of tumor suppressor genes that subsequently applied to a substantial proportion of common cancers of adults (Knudson, 1995). It appears that linking cancer and birth defects at the U.S.-Japan symposium was ahead of its time.

The symposium provided understanding of the current status of Japanese teratology for U.S. scientists among whom, for example, Nishimura's excellent studies of malformations in fetuses were not widely known. Subsequently, this work gained further support from U.S. sources. Noburo Kobayashi (Tokyo University) described results to date from a new large childhood cancer registry in the Tokyo Metropolitan Area which provided data for comparison with those from the U.S. and elsewhere. (The frequency of Wilms tumor was half that for U.S. children, a finding confirmed when data for Asian and Caucasian children were compared by I.A.R.C. (Stiller and Parkin, 1990).

Among the special features for research in Japan in 1965 were:

- The family registry system (*koseki* records), a great as-

set in follow-up studies of live births, marriages, divorces, deaths and consanguinity (Schull and Neel, 1965).

- Data from occupational records (Labor Standard Law of 1947) of value as an indicator of reproductive performance

- Dr. Nishimura's collection of human embryos, so valuable as an accurate measure of normal human embryo growth, and, from spontaneous miscarriages, the frequency of congenital malformations (Nishimura *et al.*, 1968; Shiota *et al.*, 1987)

- The Annual of Pathological Autopsy Cases in Japan has been published since 1958. It contains nationwide summaries of autopsies—about 600 a year. It has since shown, for example, that Japanese under 30 years of age have a high rate of meningeal melanoma (cited in Miller and Sugano, 1987).

- Data on atomic-bomb survivors through the binational Atomic Bomb Casualty Commission, later renamed the Radiation Effects Research Foundation, in Hiroshima and Nagasaki (Miller, 1986).

- The childhood cancer registry for the Tokyo Metropolitan area, which was followed by establishment of registries in other areas, and, derived from them, a Malignancy-Anomaly Registry (Ohmi, 1980).

- Consanguinity effects. Seven percent of marriages involve second cousins or closer, which increases the risk

of genetic disorders due to the pairing of autosomal recessive mutations (Schull and Neel, 1965).

•Migration to western countries, especially the U.S. Changes in cancer rates may indicate an environmental effect; *e.g.*, the increase in breast cancer or decrease in stomach cancer (Haenszel and Kurihara, 1968).

W. J. Schull (University of Michigan) suggested that inventiveness in the Japanese electronics industry could be applied to the automation of mass medical screening procedures, and simultaneously measure numerous biochemical constituents of body fluids. P. Kotin (National Cancer Institute) spoke of problems and techniques common to studies of cancer and congenital malformations. Soon after, experimental studies of interactions of environmental carcinogens led to the same approach in teratology.

J. Warkany (Cincinnati Children's Hospital) played a leading role at the symposium. He grew quickly in the eyes of the Japanese from a scientist known to them only by his works to a popular grand champion of teratology. In this situation, new to him and of short duration, we could see more clearly than usual how his exceptional qualities, both scientific and personal, had ignited interest in teratology in the United States and Europe. Once again his warm personality helped to unify the group.

BLANDAU'S EVALUATION ON THE MEETING

The atmosphere and unfolding of the symposium were summarized in a letter from Richard J. Blandau, M.D., Ph.D., a reproductive biologist who had been Dean of the University of Washington School of Medicine. On November 22, 1965

he wrote to me:

"I want to express my appreciation for the opportunity I had in attending the U.S.-Japan Seminar on "Epidemiological Studies into the Etiology of Congenital Malformations and Cancer." This was a very interesting and worthwhile experience for me and I want to relate a few of my thoughts concerning the value of this Meeting.

"... perhaps of greatest importance was the opportunity I had of getting to understand the feelings of some of our Japanese colleagues considering joint participation in projects of mutual interest. It seemed to me quite obvious that there was at first considerable hesitancy among the Japanese in being completely frank as to how they felt regarding ... cooperative studies. It took several days for most of us to become sufficiently acquainted with them in order to talk candidly concerning joint programs and development of areas of mutual interest. I felt that toward the end of the Conference the feeling of suspicion and concern that perhaps the American Delegation was interested in taking something from the Japanese was somewhat allayed I was impressed with the remarkable fertile field in epidemiological studies that Japan offers for investigators in many countries. I was impressed also with the importance of establishing a common baseline for methodology, terminology and nomenclature in any field of investigation where scientists of two countries could mutually participate. As you are aware, the discussions at the meeting covered a rather broad spectrum of interests and I am certain that our Japanese colleagues as well as most of us were not entirely aware of the implications of this broad base until near the end of the meeting. It was delightful to see that there was a basic common interest in



Fig. 2 Kyoto University Medical School, April 1968. Dr. Hideo Nishimura and Dr. Meredith Runner, then President of the U. S. Teratology Society.

the problems the exist for oncologists, teratologists and epidemiologists. It was clear also that there was a need to improve the methods of exchange of information between the two countries To advance this feeling of mutual cooperation it would be important to establish a number of seminars on specific problems related to the basic aspects of embryology, teratology, oncology or epidemiology. The most valuable aspect of the Seminar as far as I was concerned was the possibility of personal communication with our Japanese colleagues."

Recent discovery of this forgotten letter moved me to contact Dr. Blandau to tell him how well things have gone since the 1965 meeting, but it was two years too late. In retrospect, the seminar was long by today's standard, but had it been less than five days, it would have been unsuccessful.

SUBSEQUENT DEVELOPMENTS

A major sequel was arranged by Dr. Warkany. He had been a main advisor on the epidemic of thalidomide-induced limb deformities in children whose mothers were given the drug during pregnancy. One recommendation was that, to encourage research, international workshops be held on methods in teratology. After a successful workshop in Europe in 1966, he collaborated with Dr. Chester A. Swinyard of the Association for the Aid of Crippled Children (New York) in securing funds in the U.S. and Japan for a similar workshop for Asia and Australasia to be held in Kyoto. Dr. Nishimura was the director of the workshop assisted by James R. Miller, Ph. D., a Canadian human geneticist who was ending a year as a Visiting Research Associate with Dr. Nishimura. (Dr. Miller went on to spend most of his career in Osaka.) The workshop was held on April 1-5, 1968. There were 40 participants and 48 observers from 21 countries. The proceedings, edited by Nishimura and Miller (1969) were a gem that has gone largely undiscovered.

The organization of both meetings was extraordinary. It was there that we first saw projectionists wearing white gloves and using binoculars to make sure the slides were in focus. Details of running the seminar were smoothed by Nishimura's staff. As a recommendation in the last session, it was proposed that Nishimura hold a workshop on how to hold workshops.

Most of his research fellows went for additional training in the United States and later became departmental chairmen in several schools in Japan. The experience from these two meetings prepared me for the U.S.-Japan Cooperative Cancer Program, which began in 1974. The Interdisciplinary Area mainly concerned cancer etiology as determined by epidemiology and geographic pathology. Under its aegis, 31 small-group work-

shops were held, 1981-1996 (Miller, 1996).

Nishimura co-founded the Congenital Anomalies Research Association of Japan. He was honored in the 1980s when he was named a Fogarty Scholar at the U.S. National Institutes of Health. There he could be seen in the library at all hours, assembling information for his writing on teratology. In 1987 he was elected to membership in the Japan Academy (Sciences).

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